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Infection-induced changes in hematopoiesis

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Abstract

The bone marrow is an important site for the interrelated processes of hematopoiesis, granulopoiesis, erythropoiesis and lymphopoiesis. A wide variety of microbial challenges are associated with profound changes in this compartment that impact on hematopoietic differentiation and mobilization of a variety of cell types. This article reviews some of the key pathways that control BM homeostasis, the infectious and inflammatory processes that affect the BM, and how addressing the knowledge gaps in this area has the potential to widen our comprehension of immune homeostasis.

INTRODUCTION

The bone marrow (BM) is a critical site of immune cell development, erythropoiesis, and provides a niche for plasma cells and memory T cells. While the cell populations and structural elements in the BM are typically characterized by composition and morphology (1, 2), the application of novel imaging technologies, such as intravital imaging and laser scanning cytometry, has allowed the field to better define the microenvironments within this complex organ. Similarly, the use of conditional knock out technologies has helped to clarify the factors that maintain stem cell populations and support the development of hematopoietic precursors and immature B cells (3–6). Using these advances, recent sub-setting of stromal and precursor populations in the BM has provided insights into their behavior in the endosteal and perivascular compartments (3–6). In addition to the central role of the BM in maintaining immune homeostasis, the ability to generate and mobilize immune cells in response to infection is a key function of this system. Notably, emergency granulopoiesis and rapid mobilization of neutrophils from the BM is key for resistance to many pathogens. Similarly, increased erythropoiesis can be a physiological response to acute inflammation, but certain infections can lead to the depletion of erythroid precursors, and the development of anemia. The overarching goal of this review is to discuss the role of the BM niche in the host response to infection, illustrate the impact of infectious diseases on this compartment, and highlight some of the major questions in the field.

Hematopoiesis and the HSC niche

Hematopoiesis is the process by which hematopoietic stem cells (HSC) differentiate into immune cells through a series of lineage commitments. Lineage^{neg} Sca-1⁺ ckit⁺ cells (LSKs, reviewed extensively in (7–9)), include the earliest hematopoietic precursors in the BM with the potential to develop into multiple lineage-specific progenitors, such as common lymphoid and myeloid progenitors and megakaryocyte or erythrocytic precursors (Figure 1). Of note, only a small percentage of LSKs are HSCs; the majority of the LSK population

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represents a variety of multipotent or lineage committed cells. At steady state, this differentiation is a complex but well-ordered process, leading to the development of lymphocytes, granulocytes, and myeloid cells.

Given the diverse functions of the BM, it is not surprising that this organ is comprised of distinct anatomical compartments. For example, within the BM, HSCs are distributed primarily in or near the endosteal region or the interface between medullary bone and stromal cells (Figure 1). This is a site with a distinctive micro-anatomic circulatory system, though recent evidence indicates that perivascular niches also support HSC populations (6). The retention of HSCs in this environment is thought to promote survival and/or maintain hematopoietic progenitors in the quiescent G₀ phase of the cell cycle, allowing these cells to self renew and offering a ready pool of cells for rapid emergence (10–12). The direct interactions between vascular stromal cells and nestin-negative mesenchymal progenitors and between osteoblastic cells and HSCs themselves promote HSC survival and control niche size (5, 13).

Several chemokines and adhesion molecules, notably CXCL12 and VLA-4 (14), contribute to HSC localization and maintenance, and the local production of SCF by mesenchymal and perivascular stromal cells, as well as endothelial cells, promotes the generation and maintenance of HSCs (6). Perhaps the best-studied chemokine-receptor pair in this process is CXCL12-CXCR4 and disruption of this pathway leads to alterations in cellular retention in the BM, including mobilization of early lymphoid progenitors and HSCs (14, 15). However, these cell types occupy distinct niches, populated by discrete populations of CXCL12-producing cells (16). Thus, expression of CXCL12 by endothelial cells, perivascular stromal cells, and osteoblasts supports specific cell types within distinct niches. For example, the use of lineage-specific deletions established that nestin-negative mesenchymal progenitors, not CXCL12-abundant reticular cells (which make the majority of CXCL12 (12, 17, 18)), are the critical source of CXCL12 required to maintain HSC in the BM niche (11). This study also demonstrated that other stromal cells are key sources of CXCL12 required for survival of B cell progenitors. Of note, pre, pro, and mature B cells, as well as granulocytes, express high levels of CXCR4, though mature and immature B cell subsets are the least responsive to CXCL12. These differential sensitivities imply that later stage B cell populations are poised to traffic out of the BM, whereas early stage B cells are more receptive to signals that maintain their BM localization (19). Understanding these events has led to the utilization of blocking reagents for CXCL12 and CXCR4, which mobilize HSCs from the BM, resulting in improved harvesting of stem cells for transplantation (14, 17, 20).

Inflammation, infection, and hematopoiesis

It has long been recognized that systemic infection with a variety of bacterial, viral, and parasitic organisms can result in profound alterations in the BM, many of which appear to be part of a conserved ahost response to microbial challenge (Figure 1). For example, during malaria and toxoplasmosis (and other systemic challenges), there is an increase in granulocytes in the BM, but a transient decrease in the numbers of lymphocytes, erythrocytes, and megakaryocytes, despite low parasite burdens in this site (21–24). Increased populations of LSKs and/or HSCs in the BM are the hallmark of many experimental infections (25–31). Thus, challenge with *Plasmodium chabaudi* or *Pneumocystis carinii*, organisms not typically found in the BM, leads to increased LSK and HSC populations in the BM and circulation, followed by an increase in multipotent progenitor cells (25, 26). Similarly, murine ehrlichiosis results in increased numbers of LSK cells, though these cells appear to have a defect in their ability to differentiate (32, 33). For

many of these examples, it is unclear whether these alterations are secondary consequences of systemic inflammation or part of a coordinated host response to limit infection.

It should be noted that some of the responses associated with diverse infections are context dependent, which likely reflects different host-pathogen interactions. Thus, whether a pathogen can establish infection in the BM and which cell types it infects are relevant factors. This has led to an interest in understanding whether HSCs are inherently resistant to infection (9), however, many of these studies have used pathogens that do not commonly infect the BM or pathogens that typically require phagocytosis, a process that HSCs cannot perform. For instance, Mycobacterial species can be isolated from the BM under a variety of circumstances, that range from asymptomatic patients to AIDs patients with overt clinical disease, and a recent report highlighted that *M. tuberculosis* resides latently in mesenchymal stem cells, which are phagocytic (34). The importance of understanding these specifics is exemplified by the disparate responses associated with different viruses. Thus, the presence of the non-cytolytic lymphocytic choriomeningitis virus (LCMV) in the BM contributes to the reduced ability of HSCs to engraft in this site (35, 36). JC virus, the cause of progressive multifocal leukoencephalopathy (PML) in immune-compromised patients, can infect HSCs and B cells and is known to persist within the BM. Notably, several antibody-mediated therapies in humans that target LFA-1, VLA-4 or CD20 lead to mobilization of pre-B and B cells and CD34⁺ HSC progenitors from the BM. It has been proposed that in the context of reduced immune surveillance, these events promote the dissemination of JCV to the brain (37, 38). Cytomegalovirus (CMV) can also infect stromal and mononuclear cells within the BM, which has been linked to a reduced ability to make progenitor colonies (39). Although the examples discussed above focus on organisms found in the BM during infection, as described earlier, reductions in precursor populations can also occur with infectious challenges that do not establish in this site. For example, marked decreases in CD34⁺ hematopoietic precursors have been reported during HIV and SIV infection without detection of local virus (40–43).

Whether HSCs have an active role in immune sensing remains an open question (Figure 1) and it has been proposed that the expansion of HSC populations may serve as a component of the primary response, as well as a mechanism to replenish depleted progenitor populations (9). In adults, small numbers of HSCs appear to traffic between the BM and circulation, perhaps acting as a form of immune surveillance that can relay distal signals to the BM (44, 45). Evidence in favor of surveillance activity includes HSC expression of Toll-like receptors (TLR) (Figure 1) (9). Furthermore, TLR signaling in LSKs and other hematopoietic progenitors results in myeloid differentiation (46), while TLR9 is required in a model of HSV-1 infection for HSCs to produce dendritic cells (47). There are studies in which MyD88, the adaptor molecule involved in TLR and IL-1 signaling, has been shown to be critical for infection-induced granulopoiesis, myelopoiesis, and mobilization of these populations. Thus, infection with vaccinia virus *in vivo*, or culture of LSKs with *C. albicans in vitro* led to elevated numbers of LSKs and differentiated myeloid cells in the BM in a MyD88-dependent manner (27, 28). However, the observation that the increase in LSKs present in a model of bacterial sepsis or infection with *S. aureus* is MyD88-independent (30) highlights the gaps in our understanding of the crosstalk between the peripheral immune response and the BM compartment. Nevertheless, this literature provides a direct link between pathogen recognition and mobilization of the appropriate innate populations required to control infection.

Erythropoiesis

The suppression of erythropoiesis and development of anemia is characteristic of many infections (48). For organisms, such as *Plasmodium* and *Babesia sp*, that directly infect

erythrocytes, there is a clear link to erythrocyte destruction that can eventually lead to a depletion of erythroid precursor cells in a chronic setting. For other pathogens, such as the African Trypanosomes, the presence of parasites in the blood stream is associated with damage of erythrocytes, elevated erythrophagocytosis and, ultimately, decreased erythropoiesis (49). In other settings, severe anemia associated with the loss of erythroid precursors also has an immune component (50, 51); *Ehrlichia muris* and *Toxoplasma gondii* do not infect erythrocytes, but these distinct challenges lead to a reduction in erythroid precursors and severe anemia (32). While the cytokines IFN- γ , IL-6, and IL-15 are implicated in immune-mediated anemia (24, 52), it remains unclear whether this response simply reflects an interesting epi-phenomenon or is part of a conserved host response that limits availability of host cells for organisms that do infect erythrocytes.

Granulopoiesis and Myelopoiesis in the BM

Increased granulopoiesis within the BM is a hallmark of acute infection or inflammation in experimental and clinical settings that gives rise to short-lived neutrophils, basophils, and eosinophils (21, 23, 32, 53–56). It has long been recognized that increased circulating levels of basophils and eosinophils are characteristic of many helminth parasites, but how the immune system communicates with the BM to promote this process has been unclear. For *Trichuris muris*, a nematode parasite of mice that is restricted to the gut, this challenge leads to epithelial cell production of TSLP that induces basophil production in the BM (57). In contrast, elevated neutrophil numbers are characteristic of many bacterial infections and G-CSF promotes “emergency granulopoiesis” in the BM (58, 59). At the molecular level, steady state granulopoiesis is regulated through the transcription factor C/EBP α , whereas C/EBP β and STAT3 mediate G-CSF-dependent granulopoiesis (60, 61). Naïve mice depleted of neutrophils or injected with the adjuvant alum (which induces granulocyte mobilization) exhibit emergency granulopoiesis and proliferation of HSCs in a G-CSF- and C/EBP β -dependent manner (62). This body of work illustrates the feedback mechanisms that allow cells in the BM to respond rapidly to changes in the periphery and suggests the presence of a density sensing mechanism that regulates granulopoietic activity (62).

The BM is also an active site of myelopoiesis, leading to the production of monocytes and macrophages. BM macrophages have an important role in maintaining the HSC niche (63), yet the populations that are mobilized in response to infection have key roles in the development and resolution of inflammation, as well as acting as potent anti-microbial effectors (64). In mice challenged with *T. gondii* or *Listeria monocytogenes*, the CCR2-dependent mobilization of monocytes out of the BM is essential to control these organisms (64–67). During Ehrlichia infection, IFN- γ is required to activate macrophages to control this intracellular bacterium, but IFN- γ also contributes to the diminished hematopoietic progenitor population in the BM (33). Indeed, the ability of IFN- γ to induce SOCS3 in granulocyte-macrophage progenitors leads to reduced G-CSF signaling and a shift from neutrophil production to myeloid differentiation (68). In this context, it is tempting to speculate that systemic IFN- γ (or direct TLR signaling) provides a mechanism to tailor BM output to the class of pathogen. However, the identification of an IFN- γ -dependent atypical progenitor population of IL-7R⁺ckit^{hi} cells, with predominantly myeloid potential, that is involved in clearance of *P. chabaudi* (26), illustrates the broad effects of IFN- γ on myelopoiesis.

B cell lymphopoiesis and homeostasis

The BM is also a site of B cell development and many infections can profoundly impact this process (47, 69–74). Challenge with influenza or LCMV results in a transient decrease in pro, pre, and immature B cells in the BM, which is in part dependent on TNF α and

lymphotoxin α (71, 72). In a model of bacterial sepsis, the early depletion of B cell progenitors is delayed in MyD88-deficient mice, indicating a role for TLR or IL-1 family members (30). Although the physiological significance of these events remains to be defined, the block in B cell development correlates with reduced humoral responses to irrelevant antigens (71, 72). Interestingly, under inflammatory conditions, there is an inverse correlation between the induction of granulopoiesis and decreased lymphopoiesis in the BM (75). In one experimental system, treatment of mice with incomplete Freund's adjuvant results in an increase in granulocyte numbers, but a decline in the numbers of B (and T) lymphocytes in the BM (76). Similarly, during infection with the bacterium *E. muris*, a transient decrease in B220⁺ cells in the BM is accompanied by an increase in granulocytes (32). Insight into how these events may be coordinated is provided by the observation that, although lymphoid and granulocytic precursors express CXCR4, the disruption of the CXCL12/CXCR4 axis during inflammation leads to preferential loss of B cell precursors, potentially providing space to generate additional granulocytes required for resistance to infection (75). These studies highlight the coordinated changes that occur in hematopoietic processes in the BM during infection, that are presumably required to allow the development of appropriate responses to different classes of pathogen.

The BM as a niche for plasma cells and memory T cells

The BM also provides a niche for long-lived plasma cell populations that continually produce antibodies against previously encountered antigens. The ability of eosinophils, basophils, megakaryocytes, and stromal cells in this site to produce BlyS, APRIL, IL-6, and CXCL12, is required for the survival and retention of plasma cells (3, 4, 77–83). As noted earlier, infection can lead to alterations in many of these cell populations, and there is evidence that without eosinophils, alternative plasma cell survival niches can be established in the spleen (78). Memory CD4⁺ and CD8⁺ T cells, also reside within the BM, maintained by stromal cells that produce the cytokines IL-7 and IL-15 that act as survival and proliferative factors for these populations (84–89). In humans, it has been shown that memory T cells in the BM are more highly activated and polyfunctional than those isolated from blood, though memory T cells from blood can develop a similar phenotype after culture with IL-15 (87, 90). Thus far, it is unclear whether the profound infection-induced changes in the BM impact on the (ill defined) memory T cell and plasma cell niches or on the function of these populations. Understanding how different infections influence the homeostasis of memory cell populations in the BM may provide opportunities to manipulate these niches, and so aid in the design of vaccines that induce long lasting immunity.

Impact of systemic cytokine responses on the bone marrow compartment

While some changes that occur in the BM during certain infections may be attributed to the local presence of pathogens, perhaps the most common scenario is that the production of cytokines at distal sites affects the BM (Figure 1) (91). Thus, type I interferons can shift HSCs out of cell cycle arrest and induce proliferation and differentiation, ultimately resulting in decreased numbers of HSCs (92). In murine models of influenza or Sendai virus, production of Type I interferons in the lung leads to upregulation of antiviral genes in hematopoietic cells in the BM (93). Whether these factors are produced at sufficiently high levels in the lungs to have systemic effects in the BM or there is a mechanism to relay these signals to the BM is unclear. As discussed earlier, IFN- γ can modify myelopoiesis (26, 33, 68), and other aspects of hematopoiesis (94) and the high systemic levels of IFN- γ characteristic of many infections suggest it would have a major impact on the BM. During chronic infection with *Mycobacterium avium*, this production of IFN- γ can activate HSCs from the quiescent state (95). Additionally, IFN- γ -mediated induction of SOCS1 (an inhibitor of cytokine signaling) inhibits the ability of the cytokine thrombopoietin to activate

STAT5, which is required for HSC self renewal, leading to a reduction in the number of HSCs (94).

Systemic levels of IL-1 and TNF are also characteristic of many infectious challenges and have been linked to alterations in the BM. TNF α treatment results in a reduction in lymphocyte progenitor populations in the BM, while IL-1 β elicits increased granulocyte precursors (76). Moreover, CXCR4-deficient mice or mice treated with pertussis toxin, which blocks chemokine signaling, given IL-1 or TNF α have increased B cell and myeloid progenitors in the circulation, indicating that CXCR4-CXCL12 interactions facilitate cytokine-mediated regulation of B cell and myeloid cell retention in the BM (76). Additionally, TNF- α and IL-1, (and RANKL and M-CSF,) can induce osteoclast differentiation from mononuclear precursor cells, and subsequent inflammatory osteolysis, a complication in many infectious, inflammatory, and neoplastic diseases (96–98). Additional studies are required to understand the physiological significance of these cytokine-mediated changes in the BM and whether they impact on the development of immune responses that are tailored to specific pathogens.

The bone marrow as an immune privileged site

As described above, the BM can be a site of infection, but is sensitive to the systemic effects of microbial challenge at distal locations and it is likely that these processes could be detrimental to essential stem cell populations. Consequently, mechanisms to temper the adverse effects of inflammation on different stem cell niches may be necessary. Although the BM lacks a physical barrier to exclude immune cells, there are elements of immune privilege in this compartment that may protect progenitors from immune-mediated damage or inflammatory signals that could lead to transformation of these long-lived pluripotent cells. Notably, as much as ~25% of BM CD4⁺ T cells are FoxP3⁺ Treg cells, a much higher frequency than the 5–10% typically present in other sites. Intravital imaging of the BM of FoxP3-GFP reporters revealed that Tregs are predominantly located in or near the endosteal region, with the majority of HSCs found in close proximity to or in contact with Tregs (99). The significance of these populations in infection has not been addressed, however, in an allogeneic transfer model, depletion of Tregs prevented engraftment of an allo-hematopoietic stem cell progenitor population (99). After BM transplantation, BM T cells express a unique profile of surface markers and cytokine production, with high expression of CD44, CD62L, and CD45RB, higher levels of IFN- γ , IL-4, and IL-10, and decreased IL-2 secretion, compared to those in other sites, and an increased ability to protect from Graft Versus Host Disease (GVHD) (100). Similar findings were reported in human patients, wherein increased Tregs positively correlated with lower incidence of GVHD (100, 101). More recently, in two models of arthritic disease, Tregs in the BM inhibited TNF-mediated bone damage (102), as well as plasma cell accumulation (103). Taken together, these studies suggest that the Treg population in the BM creates a suppressive environment, which establishes a specialized niche for HSCs. Although Treg populations at other sites can be significantly altered during infection (104–106), how those in the BM are influenced by inflammation or infection and whether they preserve different niches or are resident or transient populations represent distinct gaps in our understanding of BM dynamics.

CONCLUSIONS

There have been significant advances in characterizing the effects of infection and inflammation on the function of the BM, but major gaps remain in our understanding of whether these changes impact the ability of a host to control pathogens. In some situations, such as emergency granulopoiesis or monocyte mobilization, it is easy to link these processes with resistance to infection. Alternatively, it is possible that some of the global

changes in BM cell populations reflect a shift in energetic resources from hematopoiesis to the support of effector populations required for pathogen control. Interestingly, diminished BM hematopoietic progenitor populations during infection are frequently accompanied by the development of extramedullary hematopoiesis in the spleen and liver (31, 33, 107), which may open niches and resources for the process of granulopoiesis and myelopoiesis. Additionally, the basis for and biological impact of the infection-induced blockade of B cell development in the BM remains unclear (108). In the context of infection, the presence of microbial antigens in the BM while B cells are undergoing selection could lead to the development of B cells that are tolerant to pathogen antigens or even to the deletion of pathogen-specific B cells. To the best of our knowledge, this idea has not been tested, but this phenomena may provide a mechanism to limit deleterious effects of infection on humoral immunity.

Regardless, despite dramatic changes in numerous resident BM populations in response to inflammation, the BM niche does appear to return to a normal steady-state. Whether this disruption impacts long-term hematopoiesis is not yet appreciated. Consequently, there are open questions about the processes that lead to restoration of this environment and whether they are different than those involved in the initial seeding of the BM. Understanding how restoration occurs may translate into more effective strategies to achieve BM reconstitution after irradiation, infection, or other processes that disrupt BM homeostasis. Indeed, since cancer stem cells can reside in the BM in a dormant state (109), incorrect reseeding of the BM or contamination of this immune privileged site could provide protected niches for these cells. Finally, while histological studies of the BM have provided the foundation to characterize this compartment (2), improved imaging technologies continue to improve our knowledge of the cell-cell interactions involved in the regulation of the BM niche. Combined with infectious models that have different effects on BM hematopoiesis, these technologies can be used to better understand the normal developmental processes that occur in the BM.

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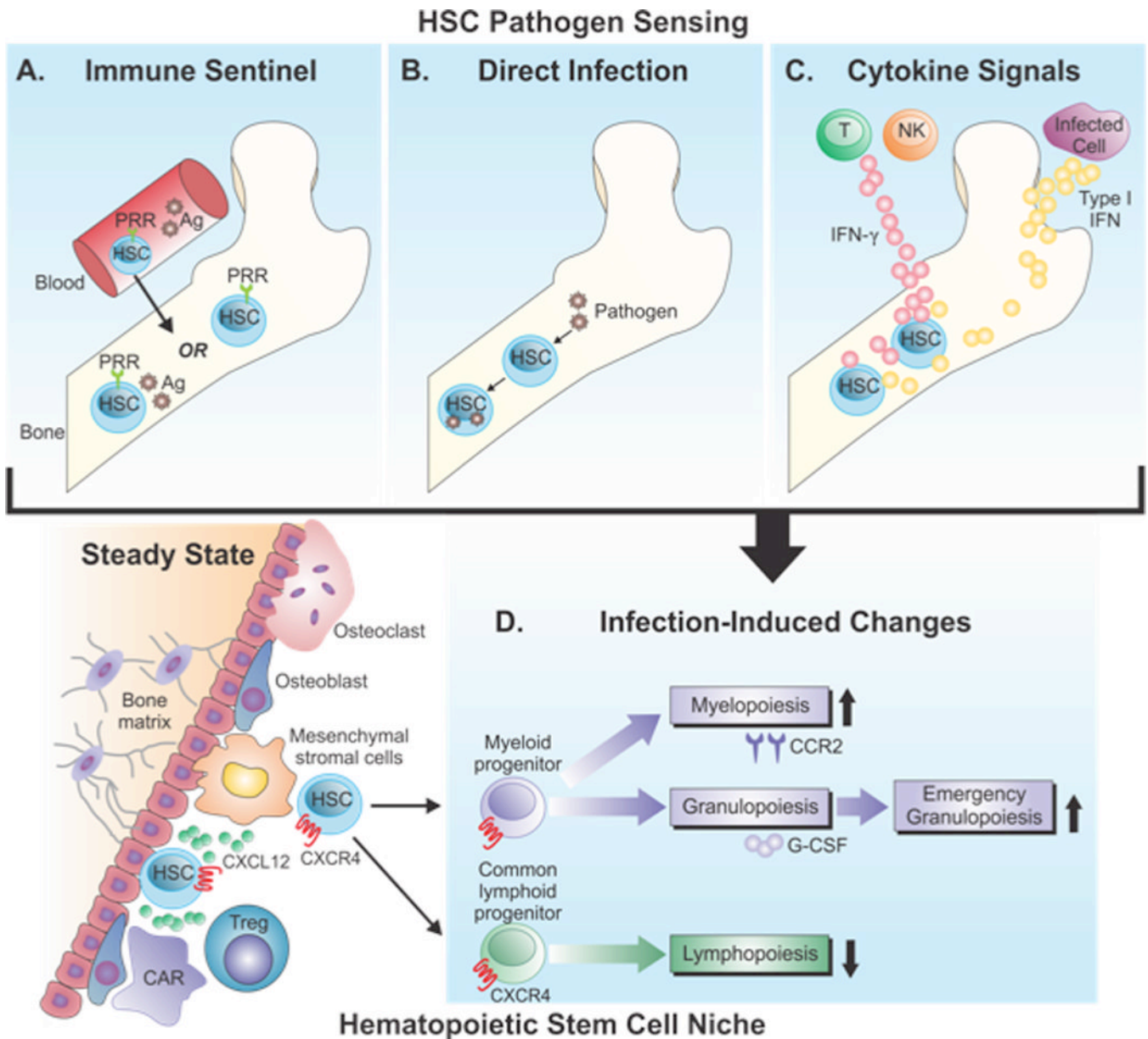
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**Figure 1.**

Hematopoietic stem cell responses to infection. (A–C). Potential routes of pathogen sensing by HSCs. (A) HSCs in the BM can express PRRs, such as TLRs, thus, when the BM is directly infected, these cells may recognize pathogen-derived antigen or immune products produced in response to infection within the BM. Alternatively, circulating HSCs in the blood expressing PRRs may recognize PAMPs and traffic back to the BM to relay these signals. (B) HSCs in the BM may be directly infected by pathogens, such as JCV and respond directly to this challenge. (C) Cytokines produced at distal sites, such as IFN- γ or type I interferons, may enter the BM and signal HSCs to initiate BM responses. Infection-induced changes in the BM (D). HSCs are maintained by stromal cells and CXCL12-CXCR4 interactions. Although HSCs are depicted here in endosteal regions, there is also evidence for their presence in perivascular niches. These cells can differentiate into myeloid or common lymphoid progenitors, which then undergo myelopoiesis, granulopoiesis, and/or

lymphopoiesis. The impact of infection on these processes is shown, with increased myelopoiesis and emergency granulopoiesis correlating with decreased lymphopoiesis.